Summary of the Office Action

The Office Action advises that a date is required for the reference identified as "Roitt, I., Brostoff, J., Male, D. Immunology 4:2.1". Moreover, the Office has rejected claims 111, 114, 115, 136, 138, 143, and 144 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Finally, claims 103, 106-111, 114-126, 130-136, 138, 139, 141, 143, and 144 stand again rejected under 35 U.S.C. § 103(a) as obvious over either of Hamann et al. (i.e., *The Journal of Immunology*, 154, 4073-4080, 1995) or Han et al. (i.e., *Journal of Cellular Physiology*, 168, 97-104, 1996), in view of Falk et al. (i.e., U.S. Patent 5,827,834).

Discussion of Amendments to the Claims

Claims 94, 101-102, 104-105, 112-113, 127-129, 137, 140, 142, and 145-170 have been cancelled without prejudice as directed to a non-elected invention. Applicant expressly reserves the right to pursue the cancelled claims in a divisional application. The remaining claims have been amended, with respect to form, so as to more particularly point out and distinctly claim the subject matter of the invention. In particular, claim 111 has been amended to clarify that the method comprises the step of "administering to the human" an effective amount of a form of hyaluronic acid. Claim 130 has been amended to clarify that the hematopoietic cells are enhanced, stimulated, and released by the administration of a form of hyaluronic acid. Claim 136 has been amended to standardize the use of the term "hyaluronic acid" in the claims instead of the equivalent term "hyaluronan". Claim 138 has been amended to correct an obvious typographical error by inserting a "t" into the word "transplantations" and also to remove "the" from before "infusion" to clarify the meaning of the method claim.

No new matter has been added by way of any of these amendments. A separate document setting forth the precise changes to the claims is attached hereto.

Information Disclosure Statement

Pursuant to the Office Action's request, Applicant submits herewith a date for the reference identified as "Roitt, I., Brostoff, J., Male, D. Immunology 4:2.1". The copyright date for the cited reference textbook is 1996. A copy of the page bearing the copyright date is enclosed herewith.

Discussion of the Indefiniteness Rejections

The Office has rejected claims 111, 114, 115, 136, 138, 143, and 144 as being indefinite under 35 U.S.C. § 112, second paragraph. These rejections are moot in view of the revisions to the claims made herein.

The Office contends that claim 111, by its preamble, is drawn to a method for the administration of hyaluronic acid but is indefinite because it fails to recite the steps involved in such a method. In view of the amendment to claim 111 to clarify the step of administering to the human an effective amount of a form of hyaluronan, this rejection, and the rejections to claims 114 and 115 dependent thereupon, are moot and should be withdrawn. The Office contends that claim 136 lacks positive antecedent basis for "the form of hyaluronan." In view of the amendments to claims 130 and 136 to clarify the administration of a form of "hyaluronic acid" instead of the equivalent term "hyaluronan," this rejection is moot and should be withdrawn. The Office contends that claim 138 lacks positive antecedent basis for "the infusion." In view of the amendments to claim 138 to remove "the," this rejection, and the rejections to claims 143 and 144 dependent thereupon, are moot and should be withdrawn.

Since all of the pending claims satisfy the requirements of 35 U.S.C. § 112, the rejections thereunder should be withdrawn.

Discussion of the Obviousness Rejection

The Office contends that claims 103, 106-111, 114-126, 130-136, 138, 139, 141, 143, and 144 are unpatentable under 35 U.S.C. § 103(a) in view of the combination of either Hamann et al. or Han et al. with Falk et al. Specifically, the Office contends that Hamann et al. teaches that hyaluronic acid (HA) stimulates growth of megakaryocyte progenitors and that HA has implications for the treatment of asthma. The Office also contends that Han et al. teaches that HA stimulates growth of CD34+ selected umbilical cord blood cells into differentiated eosinophils, and that HA may be useful for the treatment of throbocytopenias. The Office acknowledges that neither Hammann et al. or Han et al. teach the administration of HA to a patient, but contends that Falk et al. confirms that HA can be administered therapeutically, and thus it is *prima facie* obvious to one of ordinary skill in the art to modify the

method disclosed by Hamann et al. or Han et al. to stimulate the production or release of hematopoietic or dendritic cells into the blood. Applicant respectfully traverses these rejections.

Applicant considers the rejection in view of Han et al. to be inappropriate. According to the date printed on the face of the article, the cited reference (Han et al.) was accepted January 24, 1996. However, the journal issue containing the cited reference was not received into circulation until on or about June 27, 1996 (see, e.g., date stamp of June 27, 1996 by the Health Sciences Library, University of Wisconsin). The pending application claims priority to Canadian Patent 2,173,272, filed April 2, 1996. As such, Han et al. cannot be considered prior art under 35 U.S.C. § 103(a) to the instant application. Accordingly, the 35 U.S.C. § 103(a) obviousness rejection in view of Han et al. should be withdrawn. In any event, even assuming *arguendo* that Han et al. could be considered prior art under 35 U.S.C. § 103(a), the pending claims are not rendered obvious by the cited references including Han et al. (alone or in combination), as discussed below.

Contrary to the Office's assertions, neither Hamann et al. nor Han et al. discloses or reasonably suggests the use of HA as an *in vivo* therapeutic agent for stimulating the production and release of cells from bone marrow and other tissues into the blood as recited by pending claims 103, 111, 116, 124, 125, 126, 138, and claims 106-110, 114-115, 117-123, 130-131, 133-136, and 143-144 dependent thereon. In particular, Hamann et al. is directed to an *in vitro* study of the effect of HA on the proliferation of progenitor cells.

In this respect, the Hamann et al. reference discloses that HA does enhance the proliferation of purified cord blood progenitor cells. Significantly; however, the same experiments when conducted on unfractionated cell populations, which more closely resemble *in vivo* conditions, did not result in the same increase in proliferation of progenitor cells observed for the purified cells and actually inhibited their proliferation at higher concentrations (Hamann et al. in Discussion, paragraph 4, lines 4-5 and page 4077, Figure 5). Hamann et al. attributed the inhibitory effects observed for unfractionated cell populations to the possible presence of "contaminating macrophages, monocytes, and/or T cells," all of which are found *in vivo* (page 4079, left column, lines 19-22). It is noteworthy that the authors acknowledged the limitations of their studies stating: "[o]ur data are derived from an *in vitro* model of

eosinopoiesis and thus may not reflect some important component of marrow matrix molecules that may function *in vivo*" (page 4079, left column, lines 3-8). Thus, contrary to the allegation of the Office, the Hamann et al. reference teaches away from the expectation of success using HA as an *in vivo* therapeutic agent by providing evidence to support that the therapeutic benefits of HA could actually be inhibited by contaminants that are present under *in vivo* conditions. Moreover, the authors acknowledge that the umbilical cord progenitor cells studied in their experiments may "differ substantially" from marrow stem cells and that "the extent to which they can be used to model other aspects of eosinopoiesis remains to be established" (page 4079, left column, lines 25-28). In view of the above, upon review of Hamann et al., one of ordinary skill in the art would not have reasonably expected that the administration of HA *in vivo* would be an effective therapeutic agent for stimulating the production and release of cells from bone marrow and other tissues into the blood as recited by pending claims.

Han et al. is directed to the *in vitro* effects of glycosaminoglycans (GAGs), including HA, on the growth of murine megakaryocyte progenitors. Han et al. discloses that HA and several other GAGs enhanced the growth of megakaryocyte cell colonies. The authors concluded that the mechanism of action for GAGs like HA is an "indirect action through modulating the activities of growth-stimulating and/or – inhibiting factors" and that their effect is therefore "dependent on the factor(s) present in the plasma and serum" (Han et al., page 101, right column, lines 19-28). Thus, Han et al. teach that the indirect mechanism of achieving the desired end result is dependent on "factors" provided in the *in vitro* experiment. One of ordinary skill in the art would recognize that the large number of additional factors present *in vivo*, which were described by Hamann et al., were clearly not considered or controlled by Han et al., and, therefore, would doubt that HA could be an effective *in vivo* therapeutic agent for stimulating the production and release of cells from bone marrow and other tissues into the blood as recited by pending claims. The lack of expectation of success would be further compounded upon reading Hamann et al., which raises a host of concerns regarding the viability of *in vivo* results in light of the *in vitro* results, and none of those concerns are addressed by Han et al.

Even if the disclosures of Hamann et al. or Han et al. could be construed to suggest the use of HA *in vivo*, which they cannot, neither Hamann et al. nor Han et al.

discloses or reasonably suggests that HA is an effective therapeutic agent, either *in vitro* or *in vivo*, for the *release* or *mobilization* of cells from bone marrow and other tissues into the blood as recited by pending claims 103, 111, 116, 124, 125, 126, 138, and claims 106-110, 114-115, 117-123, 130-131, 133-136, and 143-144 dependent thereon. At most, Hamann et al. is directed to the effect of HA on the *proliferation* of progenitor cells and Han et al. is directed to the effect of HA on the *growth* of murine megakaryocyte progenitors. Neither reference contains any teaching or suggestion that HA can act to stimulate the *release* or *mobilization* of those cells (e.g. by de-adhesion) into the blood stream. Thus, Hamann et al. and Han et al. do not so much as suggest each and every aspect of the pending claims.

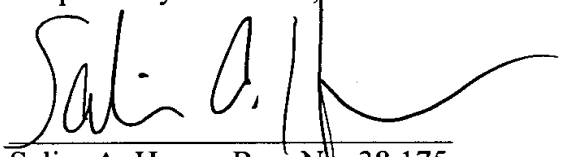
The Office relies on Falk et al. for its recitation of *in vivo* administration of HA. However, Falk et al. is not directed to the *in vivo* production/release of cells from the bone marrow into the blood. Rather, the method of Falk et al. is specifically directed to the administration of a therapeutically effective amount of a medicinal and/or therapeutic agent (e.g., Vitamin C, anti-cancer agents, anti-viral agents) to treat a disease or condition *in combination with*, or carried in, HA. The HA is administered only to "facilitate the agent's penetration through the tissue at the site to be treated" (see for example, col. 10, lines 30-37). In fact, the Falk et al. '834 patent teaches away from the use of HA as a therapeutic agent by teaching that it is a *facilitator for the transport and delivery* of therapeutic agents (col. 13, lines 59-64). Accordingly, the combination of Hamann et al. or Han et al. with Falk et al. is insufficient to suggest, let alone teach, all of the elements of the claimed invention, specifically the use of hyaluronic acid and salts thereof as a therapeutic agent to produce and release cells from bone marrow and tissue into the blood *in vivo*. Furthermore, because the Falk et al. reference is directed to a use of HA for entirely different purposes than those stated in the pending claims, there is simply no motivation to combine Hamann et al. or Han et al. with Falk et al.

Since none of the cited references discloses or fairly suggests the present invention as recited in the pending claim, the present invention is patentable over the cited references. Accordingly, the obviousness rejections should be withdrawn and the application allowed.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: July 26, 2001

CERTIFICATE OF MAILING

I hereby certify that this AMENDMENT (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: 7-26-01 Debbie Hall

IMMUNOLOGY

FOURTH EDITION

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Mosby

London Baltimore Barcelona Bogotá Boston Buenos Aires Caracas Carlsbad, CA Chicago Madrid Mexico City Milan Naples, FL New York
Philadelphia St. Louis Seoul Singapore Sydney Taipei Tokyo Toronto Wiesbaden

Publisher:	Dianne Zack
Development Editor:	Louise Cook
Project Manager:	Peter Harrison
Design:	Pete Wilder
Layout:	Rob Curran
Cover Illustration:	Richard Prime and Nick Lloyd for The Picture Palace on Alias Power Animator®
Illustration Manager:	Lynda Payne
Illustration:	Richard Prime
Production:	Jane Tozer
Index:	A. Cottingham

Published by Mosby, an imprint of Times Mirror International Publishers Limited

Printed by Grafos SA, Arte sobre papel, Barcelona, Spain

10 9 8 7 6 5 4 3 2 1 1998 1997 1996

ISBN 0 7234 2178 1

For full details of all Times Mirror International Publishers Limited titles, please write to Times Mirror International Publishers Limited, Lynton House, 7–12 Tavistock Square, London WC1H 9LB, England.

A CIP catalogue record for this book is available from the British Library.

Library of Congress Cataloging-in-Publication Data has been applied for

PATENT

Attorney Docket No. 205220

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Pilarski

Group Art Unit: 1623

Application No. 09/142,557

Examiner: K. Fonda

Filed: September 11, 1998

For: METHODS FOR CELL MOBILIZATION USING IN VIVO TREATMENT WITH HYALURONAN

AMENDMENT TO CLAIMS ON JULY 26, 2001

111. (Twice Amended) A method for administering to a human an effective amount of a form of hyaluronic acid comprising administering to the human an effective amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof having a molecular weight less than about 750,000 daltons for enhancing, stimulating and releasing hematopoietic cells and dendritic-type cells from the bone marrow and other tissues into the blood.

130. (Amended) The method of claim 111, wherein the hematopoietic cells enhanced, stimulated and released by the administration of the form of hyaluronic acid are mast cell progenitors.

136. (Amended) The method of claim 133 wherein the method of treatment includes the administration of a plurality of dosages of the form [hyaluronan] hyaluronic acid including at least one priming dosage in the amount of the form of [hyaluronan] hyaluronic acid less than about 3 mg/kg of patient body weight.

138. (Amended) A method to mobilize hematopoietic cells before and during harvesting of tissue to be used for organ [transplanations] transplantations by [the] infusion of effective amounts of hyaluronan to a patient wherein the form of hyaluronan is selected from hyaluronan and pharmaceutically acceptable salts thereof having a molecular weight less than 750,000 daltons.